(12) UK Patent Application (19) GB (11) 2 252 498 (13) A

(43) Date of A publication 12.08.1992

(21) Application No 9202311.8

(22) Date of filing 04.02.1992

(30) Priority data
(31) 91A000276 (32) 05.02.1991 (33) IT

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(51) INT CL[5]
A61K 31/22 31/535

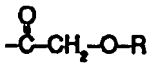
(52) UK CL (Edition K)
A5B BHA B170 B180 B42Y B423 B43Y B431 B46Y B463 B48Y B483 B54Y B544 B56Y B566 B58Y B586
U1S S1313 S2416

(56) Documents cited
None

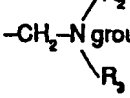
(58) Field of search
UK CL (Edition K) A5B BHA BJA
INT CL[5] A61K
Online database: CAS ONLINE

(54) Benzoyl carbinol and its esters, useful as inhibitors of angiogenesis

(57) Benzoyl carbinol and its esters, of formulae



where R is hydrogen or a  group, where R_1 is a

C_1–C_6 alkyl group or a  group where each R_2 and R_3, which may be the same or different, represents hydrogen, a C_1–C_6 alkyl group or a C_5–C_6 cycloalkyl group, or R_2 and R_3, together with the nitrogen atom to which they are bound, form a heteromonocyclic ring, or a pharmaceutically acceptable salt thereof, are useful in the preparation of a medicament for the inhibition of angiogenesis i.e. the growth of new blood vessel structures.

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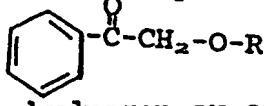
BENZOYL CARBINOL AND ITS ESTERS, USEFUL AS INHIBITORS OF ANGIOGENESIS

This present invention relates to the use of benzoyl carbinol and some of its esters to form preparations for the inhibition of angiogenesis.

The compounds which may be used according to the invention are chemical compounds which have been previously disclosed as possessing vasculotropic activity, namely a defensive or protective action on blood vessels, signally the capillaries. Such compounds are described, for instance, in U.S. Patents 2,892,865 and 3,088,947. It has now been found that the same compounds can also inhibit or suppress the growth of new blood vessels and can therefore be used as inhibitors of angiogenesis.

The present invention provides use of a benzoyl derivative which is a compound of formula (I):



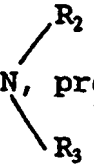
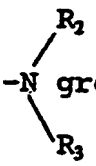
(I)

where R is hydrogen or a $-C-R_1$ group, where R_1 is a C_1-C_6 alkyl group or a $-CH_2-N$ group where each R_2 and R_3, which may be the same or different, represents hydrogen, a C_1-C_6 alkyl group or a C_5-C_6 cycloalkyl group, or R_2 and R_3, together with the nitrogen atom to which they are bound, form a heteromonocyclic ring, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament useful for the inhibition of angiogenesis.

Alkyl groups in the above formula may contain a

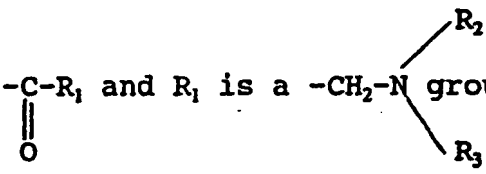
linear or a branched chain. Preferably an alkyl group contains 1 to 4 carbon atoms.

When in compounds of formula (I) R is a  group where R_1 is a C_1-C_6 alkyl group, this is preferably a $-CH_3$ group or a $-C(CH_3)_3$ group.

When in compounds of formula (I) R represents a  group where R_1 is  , preferred values of R_2 and R_3 include one of R_2 and R_3 being hydrogen and the other being hydrogen, C_{1-4}alkyl, particularly isopropyl, or a C_5 or C_6 cycloalkyl group, particularly cyclohexyl. The  group may therefore be, for instance, an amino, isopropylamino or cyclohexylamino.

When $-NR_2R_3$ is a heterocyclic group it is preferably an optionally substituted five- or six-membered unsaturated or saturated heterocyclic ring containing at least one nitrogen atom and may optionally contain one or more further heteroatoms, such as nitrogen, oxygen or sulfur. Preferred substituents are C_1-C_4 alkyl, particularly methyl, and amino. More preferably, the heterocyclic group is tetrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, triazinyl, morpholino or pyrrolidino group. Morpholino, methylmorpholino,

aminomorpholino and pyrrolidino are particularly preferred heterocyclic groups.

Examples of pharmaceutically acceptable salts of compounds of formula (I) are the salts of compounds of formula (I) where R is  and R_1 is a $-CH_2-N$ group as defined above, with pharmaceutically acceptable salts whether inorganic (e.g. hydrochloric, sulfuric or phosphoric acid) or organic (e.g. tartaric, citric, maleic, methanesulfonic, or ascorbic acid).

The salification of compounds of formula (I), for instance with the acids listed above, tends to increase the water solubility of those compounds and make them better suited, for instance, for intramuscular administration.

The following are examples of specific compounds according to the invention:

benzoylcarbinol;

benzoylcarbinol acetate;

benzoylcarbinol trimethylacetate;

benzoylcarbinol aminoacetate;

benzoylcarbinol morpholino acetate;

benzoylcarbinol morpholino acetate tartrate;

benzoylcarbinol morpholino acetate ascorbate;

benzoylcarbinol morpholino acetate hydrochloride;

benzoylcarbinol aminoacetate tartrate;

benzoylcarbinol aminoacetate ascorbate; and

benzoylcarbinol aminoacetate hydrochloride.

As noted before, the chemical compounds of the invention are known substances, and as such they can be obtained by known methods, such as those described in the U.S. Patents quoted earlier in this text.

In particular, compounds of formula (I) where R is other than hydrogen can be obtained by the usual methods described in organic chemistry for the esterification of primary alcohols. Likewise conventionally, one can achieve the salification of compounds of formula (I) containing a salifiable group.

The compounds of the invention have been found to be active as inhibitors of angiogenesis.

An inhibitor of angiogenesis is defined as a drug agent capable of inhibiting or suppressing the growth of new blood vessels.

Accordingly, the compounds of the invention are useful for treating a number of pathologic conditions in mammals, including man, where the development of new blood vessels is harmful and therefore unwanted. Such conditions include, for instance, chronic inflammation, diabetic retinopathy, psoriasis, rheumatoid arthritis, and tumoral growth.

The compounds of the invention can be administered, for instance, particularly in the treatment of cancer, alone or associated with other drug agents such as, for instance, heparin, suramine, polysulfate cyclodextrins, or

derivatives thereof.

The inhibitory activity of the compounds of this invention on angiogenesis is demonstrated, for instance, by the fact that such substances have been found active in the chorioallantoid membrane test described by Folkman [Nature, 297, 307 (1982)]. Thus, for instance, in that test the compounds of the invention benzoylcarbinol trimethylacetate and benzoylcarbinol morpholino acetate have been found to inhibit vascularization in doses of 50 µg/pellet.

The compounds of the invention can be administered by the usual routes, e.g. parenteral, such as intravenous injection or infusion, intramuscular, subcutaneous, topical, or oral dosing.

Dosages will depend on the patient's age, weight, clinical status, and selected route of administration. Thus, for instance, the appropriate dosage for administration to an adult patient may vary from approximately 0.5 to approximately 100 mg per dose, for one to four doses a day. As said before, the invention concerns the use of compounds of formula (I) in the preparation of a medicament intended to inhibit angiogenesis.

The medicament may be for example a pharmaceutical composition containing a compound of formula (I) as active substance, and one or more pharmaceutically acceptable excipients and/or carriers.

The pharmaceutical compositions are usually prepared by conventional methods and are then administered in a

suitable pharmaceutical dosage form.

Thus, for instance, solutions designed for intravenous injection or infusion may contain as carrier, for instance, sterile water; or, preferably, they may be in the form of sterile aqueous isotonic saline solutions.

Suspensions or solutions designed for intramuscular injection may contain, along with the active substance, a pharmaceutically acceptable carrier such as, for instance, sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, plus an appropriate amount of lidocaine hydrochloride if desired.

In pharmaceutical dosage forms designed for topical application, e.g. creams, lotions or pastes for dermatological use, the active substance may be compounded with conventional oleaginous excipients or emulsifying agents.

Solid oral dosage forms, e.g. tablets and capsules, may contain, along with the active substance, diverse diluents, e.g. lactose, dextrose, saccharose, cellulose, corn or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate and/or polyethylene glycols; binding agents, (e.g. starches, gum arabic, gelatin, methylcellulose, carboxy-methylcellulose, polyvinylpyrrolidone; disaggregants, e.g. a starch, alginic acid, alginates, sodium starch glycolate; effervescent mixtures; dyes; edulcorants; wetting agents e.g. lecithins, polysorbates or laurylsulfates; and more generally, such

nontoxic and pharmacologically inert substances as are currently used in galenical formulations.

Said pharmaceutical compositions may be prepared by generally known methods, e.g. by processes of mixing, granulation, tablet coating or sugar-coating.

A method for treating pathologic conditions in which the growth of new blood vessels is considered harmful e.g. chronic inflammation, diabetic retinopathy, psoriasis, rheumatoid arthritis, and tumors, in mammals including man, may be carried out by administration to said mammals of a composition as described above. The following examples of formulation illustrate but do not limit the invention.

Intramuscular injection 40 mg/ml

An injectable pharmaceutical dosage form can be prepared by dissolving 40 g of benzoylcarbinol morpholino acetate in water for injection (1000 ml) and distributing into sealed ampoules of 1 to 10 ml each.

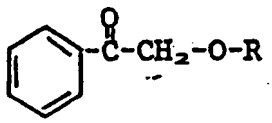
Capsules 100 mg

Benzolycarbinol trimethylacetate	100 mg
Lactose	248 mg
Corn starch	50 mg
Magnesium stearate	2 mg
Total	400 mg

Fill into hard-gelatin capsules.

CLAIMS

1. Use of a benzoyl derivative which is a compound of formula (I)



(I)

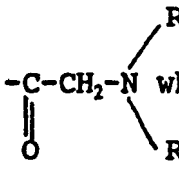
where R is hydrogen or a $-\overset{\overset{O}{\|}}{C}-R_1$ group, where R_1 is a C_1-C_6 alkyl group or a $-CH_2-N\begin{matrix}R_2\\R_3\end{matrix}$ group where each R_2 and R_3, which may be the same or different, represents hydrogen, a C_1-C_6 alkyl group or a C_5-C_6 cycloalkyl group, or R_2 and R_3, together with the nitrogen atom to which they are bound, form a heteromonocyclic ring, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament useful for the inhibition of angiogenesis.

2. Use according to claim 1 in which in formula (I), R is hydrogen.

3. Use according to claim 1 in which R is $-\overset{\overset{O}{\|}}{C}-R_1$ where R_1 is $-CH_3$ or $-(CH_3)_3$.

4. Use according to claim 1 in which R is $-\overset{\overset{O}{\|}}{C}-R_1$ where R_1 is $-CH_2-N\begin{matrix}R_2\\R_3\end{matrix}$ where one of R_2 and R_3 is hydrogen and the other is hydrogen, C_{1-4}alkyl, or cyclohexyl.

5. Use according to claim 1 in which R is



where R_2 and R_3, together with the nitrogen atom to which they are attached form a morpholino or pyrrolidino group.

6. Use as described in claim 1 above, where the derivative is:

benzoylcarbinol;

benzoylcarbinol acetate;

benzoylcarbinol trimethylacetate;

benzoylcarbinol aminoacetate;

benzoylcarbinol morpholino acetate;

benzoylcarbinol morpholino acetate tartrate;

benzoylcarbinol morpholino acetate ascorbate;

benzoylcarbinol morpholino acetate hydrochloride;

benzoylcarbinol aminoacetate tartrate;

benzoylcarbinol aminoacetate ascorbate; or

benzoylcarbinol aminoacetate hydrochloride.

7. Use according to claim 1, where the derivative is benzoylcarbinol trimethylacetate.

8. Use according to claim 1 where the derivative is benzoylcarbinol morpholino acetate or a pharmaceutically acceptable salt thereof.

9. Use according to any one of the preceding claims where the medicament is intended for the treatment of chronic inflammation, diabetic retinopathy, psoriasis,

or rheumatoid arthritis.

10. Use according to any one of claims 1 to 8 where the medicament is intended for the treatment of a tumor.

(i) UK Classification (Edition K)	A5B (BHA, BJA)	
(ii) Int Cl (Edition 5)	A61K	J F JENKINS
Databases (see over) (i) UK Patent Office		**Date of Search**
(ii) ONLINE DATABASE: CAS-ONLINE		13 APRIL 1992

Documents considered relevant following a search in respect of claims 1 TO 10

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
	NONE	

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family, corresponding document.

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